ABSTRACT

Nutritional supplementation as demonstrated in the Age-Related Eye Disease Study has helped to delay the progression of age-related macular degeneration (AMD), but it is not curative. Therefore, prevention of advanced AMD (choroidal neovascularization or geographic atrophy) is desirable for avoiding or minimizing the central vision loss that may progress to blindness in patients with AMD. Epidemiological investigations have identified certain risk factors for AMD, including some that are modifiable. These findings suggest certain behaviors that may help to delay disease progression. This article reviews epidemiological findings and summarizes continuing clinical investigations of the role of antioxidants and laser treatment in preventing disease progression.


The clinical hallmark of age-related macular degeneration (AMD) is the appearance of drusen, diffuse thickening of the basement membrane of the retinal pigment epithelium and Bruch’s membrane. However, the pathobiology responsible for the drusen linked to early AMD is not well understood. Indeed, the relationship between AMD and drusen remained controversial well into the 1970s. Since then, larger areas of large soft drusen have been conclusively linked to an increased risk of progression to advanced AMD, providing a roadmap for clinicians to assess the disease state.

Age-Related Eye Disease Study (AREDS)-type nutritional supplementation for the treatment of patients with intermediate or advanced dry AMD helps to reduce vision loss and progression of dry AMD to advanced AMD. Prevention of AMD and specifically prevention of choroidal neovascularization (CNV) is a preferred clinical approach. By gaining an understanding of the risk factors associated with AMD and current areas of clinical investigation, clinicians can better advise patients about modifiable behaviors that may be beneficial.

RISK FACTOR ASSOCIATIONS

Population-based epidemiologic studies and clinical observations indicate that geographic atrophy or neovascular AMD are rare before age 55 years, become more common in persons 75 years or older, and are less common in African Americans than whites. Although AMD is not entirely heritable, a familial predisposition toward the disease is reported. Several risks factors have been identified, such as hypertension and cardiovascular disease, but some studies report contradictory factors associated with neovascular AMD and geographic atrophy. Such contradictions suggest that these factors may not contribute significantly to the pathobiology of the disease and that differences in associations may be a function of different pathogenic pathways for geographic atrophy and neovascular AMD. Very recently, an association with a blood factor, complement factor H, has been reported by more than 1 group.

In addition to age and family history, the area and number of drusen have been reported to be a risk factor for disease progression. Cigarette smoking is another significant risk factor for AMD, with current smokers shown to be at higher risk of incident AMD than past...
smokers and those people who never smoked. This result may be because of the effect of smoking on antioxidant metabolism and choroidal blood flow. Other lifestyle choices are also now thought to play a role, suggesting that patients can modify certain behaviors to deter disease progression. For example, a study by Seddon et al found higher waist circumference was associated with a 2-fold increased risk for advanced AMD, with a significant trend for increasing risk with a greater waist circumference \( (P = .02) \). Increased physical activity tended to be associated with a reduced rate of progression (25% reduction for 3 times per week vigorous activity vs none; \( P = .05–.07 \)). In a separate analysis, Seddon et al reported that total fat consumption was associated with higher risk of advanced AMD, with a relative risk (RR) of 2.90 (95% confidence interval [CI]). Animal fat intake was associated with a 2-fold increased risk of progression (RR, 2.29; 95% CI); higher vegetable fat consumption had a stronger relationship with increased risk of AMD progression (RR, 3.82; 95% CI). Saturated, monounsaturated, polyunsaturated, and transunsaturated fats increased the likelihood of progression. Whereas baked goods increased the risk of AMD progression 2-fold, consumption of fish and nuts were shown to be protective.

The findings by Seddon et al support those findings reported previously by Cho et al, who analyzed data from the Nurses’ Health Study of more than 70,000 subjects and reported an association between total fat intake and risk of AMD. In this study, high linolenic acid intake was associated with a 49% increased risk of AMD, and high docosahexaenoic acid (DHA; an omega-3 fatty acid produced by algae and found in fish or nutritional supplements) was associated with a 30% reduced risk of AMD. In these findings, fish intake was again reported to be beneficial. In a recently published study, Seddon et al reported an association between elevated C-reactive protein levels and advanced macular degeneration, implicating a possible role for inflammation in the pathogenesis of the disease.

Epidemiological associations between modifiable behaviors and disease serve as useful fodder for clinicians to promote positive lifestyle choices. Sound advice for patients for the prevention of AMD (and a host of other health problems) is to stop smoking, exercise regularly, and avoid unhealthy fats.

**ONGOING INVESTIGATIONS**

To confirm observational reports that antioxidants may delay progression of AMD and vision loss, researchers recently completed a large randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc referred to as the AREDS study. Data from this investigation show a reduction in moderate vision loss (19% at 7 years), in addition to a 25% reduction in progression to advanced AMD or geographic atrophy in patients taking a combination of antioxidants and zinc. However, supplements were not found to restore lost vision and showed no beneficial effect for cataract. Some evidence from this study suggested that higher levels of lutein, zeaxanthin, DHA, and omega-3 fatty acids may be beneficial for AMD. One systemic review of trials in this area reported a modest protective role for antioxidants plus zinc in the prevention of progression of established disease and vision loss over 6 years compared with placebo, but not for prevention of AMD entirely. Furthermore, potential harmful effects of long-term supplementation with high-dose vitamins cannot be ruled out, and the pill burden may be a deterrent to compliance. A follow-up investigation to the AREDS study, the AREDS-2 trial, will investigate a combination of lutein and zeaxanthin with DHA to establish further whether these antioxidants are helpful in preventing AMD progression.

Another area of clinical investigation is the use of laser treatment of drusen. Although some investigators report reduction of drusen with laser treatment, a concomitant reduction of advanced AMD risk has not been conclusively demonstrated. A larger randomized controlled trial showed potential harm from the development of CNV when low-intensity laser is used. In a subgroup of subjects with unilateral drusen, laser treatment significantly increased the incidence of CNV (estimated 12 month incidence 10/59 [17%] with laser treatment vs 2/61 [3%] with no laser treatment; \( P < .05 \)). The trial was ended prematurely as a result of these findings. Additional trials are ongoing or planned, but laser treatment of drusen remains entirely investigational at this point in time. We anticipate results from 2 laser prophylaxis trials, the Prophylactic Treatment of AMD Trial and the Complications of AMD Prevention Trial in 2005 and 2006. At this time, laser treatment of drusen is not recommended outside a clinical trial.

Rheopheresis blood filtration is another area of ongoing investigation in AMD. This is a form of therapeutic plasma apheresis that uses 2 in-line hollow-fiber membrane filters to remove circulating high...
molecular weight plasma components. It is thought that these macromolecules may be impeding local circulation in the choroid. The first filter separates the blood plasma from the red and white blood cells. The plasma then passes through the second filter where the larger plasma molecules are trapped. Some of the targeted macromolecules include α2 macroglobulin, von Willebrand factor, fibrinogen, immune complexes, lipoprotein a, and low-density lipoprotein cholesterol. Very early data show actual improvement in short-term visual acuity for patients undergoing rheopheresis, and patient recruitment for a controlled clinical trial has begun. At this time, there is no conclusive evidence for safety or efficacy of rheopheresis for AMD.

One of the most important preventive trials taking place at this time explores the use of anecortave acetate, an engineered synthetic angiostatic cortisone with an excellent safety record. In this study, anecortave acetate is administered to patients every 6 months through an extraocular posterior juxtascleral depot injection to place the drug at the target tissue—the posterior macular sclera. As an engineered steroid, the agent affects the nucleus of vascular endothelial cells by altering genetic transcription and translation to reduce cell migration. In addition, the treatment reduces the proliferation and enzymatic degradation of the basement membrane and extracellular matrix associated with CNV. The study drug is being administered to patients with established neovascular AMD whose fellow eyes have 5 or more drusen (or confluent drusen) and focal hyperpigmentation. By design, the study includes eyes at highest risk for the development of neovascular AMD to determine whether the disease can be prevented entirely. Although neither safety nor efficacy of anecortave acetate have been demonstrated, patients have been rapidly enrolling in this study with the hope that vision may be preserved in the at-risk eye before onset of disease. The United States Food and Drug Administration recently issued an “approvability letter” for this drug based on treatment studies. The efficacy of anecortave acetate prophylaxis will not be known most likely until approximately 5 years from now, as enrollment is underway and will not be completed until later this year.

CONCLUSIONS

The holy grail in this devastating disease is prevention. Already the leading cause of irreversible blindness among the elderly, AMD can only increase in prevalence with the aging of the American population. A growing understanding of AMD has led to the development of new treatments that can temper progression of the disease. Although prevention of the disease remains our ultimate goal, unfortunately it is also an elusive goal. We eagerly anticipate results from ongoing investigations in this field.

DISCUSSION

**Dr Schachat:** Multiple vitamin and mineral formulations marketed for the prevention of AMD require patients to take 2 pills 4 times a day. A newer formulation is a gel cap taken twice a day. Will the absorption of the gel cap nutrients be comparable to other formulations?

**Dr Regillo:** A pharmacokinetic profile of the gel caps would answer that question.

**Dr Rosenfeld:** One of the greatest limitations of recommending the AREDS vitamin formula is that patients have to take 2 in the morning and 2 at night. Many of my patients find it difficult to remember to take the vitamins and also find them difficult to swallow.

**Dr D’Amico:** There are substantial objections to the data analysis methods used in the AREDS study. Nonetheless, because there is biologic plausibility for using nutritional supplementation, and in the absence of other proven prophylaxis, it makes sense to recommend the supplements to appropriate patients. In terms of whether patients take 100% of the recommended dose, I don’t think there’s a scientific rationale for making a strong case that 4 pills are effective and 3 pills are not. I am looking forward to reports from the AREDS-2 trial, which will hopefully tell us more than the data from AREDS-1. However, until we see the AREDS-2 data, we have to use the best available evidence from AREDS-1.

**Dr Gragoudas:** Although I acknowledge the limitations of the AREDS-1 study design, I also recommend that patients take nutritional supplements because the study findings represent the best available information. I find that my patients generally comply with the dosing, despite the fact that they are elderly and are usually taking multiple medications. I would recommend that they take the formulation that was used in the AREDS trial. If an individual patient has difficulty with the pill burden, I would have no problem switching to the gel caps. Absorption studies probably aren’t necessary.

**Dr Rosenfeld:** I think we can learn something from our colleagues who found that patients with glaucoma don’t actually use the drops as frequently as they...
report. I suspect that our patients are behaving similarly; they want to please us and tell us they are taking their vitamins, but they are most likely not taking the regimen that we recommend.

Dr D’Amico: How would you explain the powerful association between smoking and progression of a macular degenerative lesion?

Dr Gragoudas: Macular degeneration is secondary to vascular abnormalities. Thus, cardiovascular risk factors likely also increase the risk of AMD. It follows, then, that statins may have a role in preventing AMD. This is an area worthy of further study.

Dr D’Amico: Dr Ho mentioned a reported association between elevated C-reactive protein levels and advanced macular degeneration, implicating a potential role for inflammation in the pathogenesis of the disease.

Dr Gragoudas: This too suggests an association between known cardiovascular risk factors, such as elevated C-reactive protein levels, and risk factors for AMD.

Dr Rosenfeld: Getting back to the role of smoking in AMD, it seems that smoking aggravates every human disease state. This is likely because of a wide range of effects, including the impact of smoking on blood oxygen levels, the immune system, or overall tissue integrity. It is important to recognize that we don’t know how smoking interacts with vitamin supplements. Nonetheless, we very commonly recommend a smoker’s version of the AREDS vitamins without vitamin A. We have assumed that vitamins are beneficial to smokers with AMD, without really knowing the facts. What we do know is that quitting smoking may be the one lifestyle alteration that can most dramatically impact disease progression.

Dr Ho: Given that quitting smoking can be extremely difficult, as ophthalmologists we have a somewhat unique leverage. Whereas the internist can only warn patients about cardiovascular risks and future health problems, we can talk to our patients about ocular risks. People truly value vision, and sometimes patients will discontinu e smoking based on our discussions with them.

Dr Schachat: Patients are very eager to prevent the progression of AMD. Do you actively recommend anything other than vitamins and minerals and smoking cessation?

Dr Regillo: As Dr Ho stated earlier in this discussion, people value vision and are afraid of vision loss. Those people who have experienced vision loss in one eye are most likely to be willing to take vitamins twice a day for a long time. However, they may also be telling us that they are taking the vitamins as directed when they are not. It is important to educate patients about their individual risks for vision loss and what they can do to prevent it. Beyond the vitamin supplements and smoking cessation, I address cardiovascular risk factors, such as hypercholesterolemia, lifestyle, and diet, and advise patients to consult their primary care physicians. Patients who don’t visit their primary care physicians regularly may be prompted to do so if we tell them it can positively impact their vision.

Dr Schachat: Do you advise patients who are classified as category 2 disease and may have 1 or 2 drusen in each eye not to take the AREDS supplements?

Dr Regillo: I explain that their risk of having advanced vision loss is 3% or less, and that there is no evidence to support their use of the full AREDS formula. It’s an expense and there is a risk of genitourinary-related side effects related to the high zinc intake.

Dr Rosenfeld: I ponder the other extreme: Do we encourage patients who have advanced non-neovascular disease in both eyes to take the vitamins? Or, are the supplements of any benefit to a patient with neovascular AMD in one eye and a disciform scar in the other?

Dr Ho: I also consider that question. I try to get a sense of how much control patients will feel if they continue taking the vitamins. The risks associated with taking these vitamins are low. However, there are costs involved; the cost of taking away any remaining hope for a patient is higher. And, we all know that depression is a reality for people with AMD. If patients feel they need to take the vitamins, I will agree to it.

Dr Schachat: AREDS did not address this question because the study did not enroll patients with neovascular AMD in both eyes. However, during the course of 8 years of follow-up, patients did develop neovascular disease in the nonstudy eye. Although the sample sizes were not large enough to demonstrate statistical significance, the study did show some trends for reduced vision loss in patients with neovascular disease taking supplements. However, the study was not designed to evaluate prevention of progression of neovascularization and the data are not conclusive.

How often do you ask patients in the highest risk groups—those patients with CNV or scar in one eye and large drusen with pigment changes in the other eye—to come in for an examination?

Dr Regillo: I recommend that category 4 patients have their eyes checked once every 6 months. There are no data that suggests I am likely to detect the disease earlier with more frequent visits. However, I’d like to raise another question: How often do you instruct your
patients to use an Amster grid? I’ve had category 2 patients tell me that their eyecare providers instructed them to use an Amster grid. I only give an Amster grid to patients with category 3 or worse disease and ask them to look at it weekly.

Dr Rosenfeld and Gragoudas: I examine category 4 patients every 6 months, and emphasize that they should be alert to the signs and symptoms of early neovascularization. Monitoring at home is also crucial.

Dr Regillo: I imagine that lesion subtype plays a role because some lesions may be more symptomatic than others. Another contributing factor may be whether the lesion occurred in the nondominant eye.

Dr D’Amico: In my own practice, it would be relatively rare for an asymptomatic patient to come in for a 6-month or annual examination and suddenly become a treatment candidate, as compared to a patient who is having a problem and is then examined.

Dr Rosenfeld: In the CAPT (Complications of Age-Related Macular Degeneration Prevention Trial) study, fluorescein angiograms were routinely given at the follow-up examination, whereas in clinical practice we use them less routinely. Therefore, how many of the new CNV cases would have been identified with only routine biomicroscopic examination?

Dr Schachat: I would assume that most of the time we detect CNV with biomicroscopic examination, although lesions are sometimes subtle.

Dr D’Amico: Shifting topics to the use of laser to drusen, Dr Ho explained that this treatment is potentially harmful, although its efficacy is still being studied. Do you feel that there is any role for laser to drusen outside of the ongoing clinical trials?

Dr Ho: No.

REFERENCES